PATENT SPECIFICATION (11) 1 539 771

1 539 771

(21) Application No. 36121/76 (22) Filed 1 Sept. 1976

(23) Complete Specification filed 21 Nov. 1977

(44) Complete Specification published 7 Feb. 1979

(51) INT CL² A61K 33/40

(52) Index at acceptance

A5B 170 244 246 24X 24Y 26Y 272 27X 27Y 285 28Y 381 38Y 390 401 402 406 40Y 411 41Y 432 43Y 480 482 485 48Y 492 49Y 551 55Y 576 57Y 586 58Y 616 61Y 64X 64Y J

(72) Inventor HARRY FITTON

(19)

(54) DERMATOLOGICAL COMPOSITIONS

(71) We, QUINODERM LIMITED, a British Company of Manchester Road, Hollinwood, Oldham, Lancashire OL8 4PB, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to dermatological compositions containing hydrogen peroxide. The invention is primarily concerned with such compositions for human therapeutic use. It is however to be understood that the invention is not intended to be limited to such use and thus for example compositions according to the invention may be used in a veterinary rather than a human context and/or may be of cosmetic rather than therapeutic effect.

Hydrogen peroxide has a well known therapeutic and cosmetic effect in a dermatological context due to its ability to make available free oxygen in contact with the skin. Further, hydrogen peroxide is a readily available and relatively inexpensive substance which need not only be used in small quantities for dermatological purposes due to the high proportion of available oxygen which it contains. In these respects therefore, hydrogen peroxide is a desirable substance for dermatological use. Hydrogen peroxide has not however found wide acceptance in proprietary dermatological compositions due to certain disadvantages which arise with the use of the substance, in particular due to the fact that the substance is very unstable, due to the possible damage to skin tissue which may be caused if the skin is exposed to an unduly large amount of hydrogen peroxide, and due to the fact that hydrogen peroxide has a high surface tension and therefore tends not to spread easily on the skin and make intimate contact therewith.

An object of the present invention is to provide a dermatological composition containing hydrogen peroxide with which the above mentioned disadvantages can be avoided or at least appreciably reduced.

According to the invention therefore there is provided a dermatological composition in the form of a cream, lotion or gel comprising an oil medium dispersed in an aqueous medium, said aqueous medium containing hydrogen peroxide and a buffer to maintain the pH of the composition at less than 7.

With this composition, due to the incorporation of the hydrogen peroxide in an oil-in-water preparation and due to the presence of the acid buffer it has been found possible to achieve surprisingly good dermatological activity with a relatively small proportion of hydrogen peroxide (say no greater than 3.75% by weight) whereby the possibility of damage to the skin tissue can be avoided or at least appreciably minimised, and also to achieve a remarkable stability to the extent that such dermatological activity can be expected to be retained after an appreciable period of storage. For good stability the nature and amount of buffer is preferably such as to give a pH in the range 2.5 to 6.5. The use of hydrogen peroxide in a cream, gel or lotion also enables easy and intimate application to the skin.

In accordance with a preferred embodiment of the invention, the composition is an oil-in-water cream preparation of the "vanishing" cream kind in which a small proportion of an oil medium is dispersed as an emulsion in a high proportion of an aqueous medium. Such cream preparation when applied to the skin does not have an oily or greasy feel and is therefore particularly suitable for treating distressing skin conditions such as acne.

The oil medium may be of any suitable form appropriately selected such that it is dermatologically innocuous and such that it is compatible with the remaining constituents of the preparation. Thus, for example, the oil medium may comprise a saturated hydrocarbon wax and an emulsifying wax. The hydrocarbon wax

may be one or more substances selected from hydrocarbons of general formula

$$C_nH_{2n+2}$$

and fatty acids of general formula

$$C_nH_{2n+1}COOH$$

and may comprise for example hard paraffin wax, liquid paraffin Adeps Solidus, white or yellow soft paraffin wax. Preferably the substance known as "white soft paraffin wax" which is a semi-solid mixture of hydrocarbons obtained from petroleum and having a melting point in the range 38°C to 56°C is used. The emulsifying wax may be any suitable ionic or non-ionic substance. Thus for example it may be a non-ionic substance of general formula

$$R—CH_2—O(CH_2 . CH_2 . O)_nH$$

and may be for example the substance known as Lanbritol Wax N21 (Trade Mark) which is a mixture of 86% by weight cetostearyl alcohol with 14% by weight of a non-ionic emulsifier. The cetostearyl alcohol contains 30% by weight cetyl alcohol and 70% by weight stearyl alcohol and the emulsifier is a cetyl-oleyl ether of polyethylene glycol having a mean chain length of 14 ethylene oxide units. Alternatively, the substance known as Cetomacrogol Emulsifying Wax BPC may be used. This substance comprises a compound having the formula

$$CH_3(CH_2)_m—O—CH_2(CH_2·O.CH_2)_nCH_2O-H$$

where m is 15 to 17 and n is 19 to 23, and four times its weight of cetostearyl alcohol. Alternatively, an anionic emulsifying wax may be used, such as Emulsifying Wax BPC, comprising 9 parts by weight cetostearyl alchol and 1 part sodium lauryl sulphate or other sodium salt of a sulphated primary aliphatic alcohol or any mixture of salts.

With regard to the buffer, as mentioned this may be such as to maintain the pH at 2.5 to 6.5 and any suitable buffer may be used for this purpose. Thus, for example, there may be used an acid such as lactic acid, citric acid, tartaric acid, maleic acid, hydroxysuccinic acid with an acid salt, said acid salt may be any of sodium and potassium acid phosphate, sodium and potassium acid citrate, sodium and potassium acid tartrate.

In addition, if desired the composition may incorporate one or more of: a chelating agent, starch, a pharmaceutically active quinoline derivative, chlorhexidine gluconate, urea, hydrocortisone, a corticosteroid, and other substances which provide an auxiliary therapeutic or cosmetic effect or act to improve (possibly synergistically) the therapeutic or cosmetic effect of one or more of the other constituents.

With regard to the quinoline derivative, the composition may incorporate such a derivative which is a bactericidal and keratolytic agent for example a substance selected from potassium 8-hydroxyquinoline sulphate, 8-hydroxyquinoline sulphate, iodochlorhydroxyquinoline, diiodohydroxyquinoline and di(8-hydroxy-7-iodoquinoline-5-sulphonate).

With regard to the chelating agent, this may be provided for the purpose of minimising any loss of activity and discoloration of the quinoline derivative, where such derivative is provided, and in order to minimise any loss of available oxygen from the peroxide particularly due to the presence of metal ions in the preparation. Such chelating agent may be any suitable substance for example ethylenediamine tetra-acetic acid (EDTA) or any of the disodium, trisodium, dipotassium and tripotassium salts of EDTA.

Starch may be incorporated in the preparation for the purpose of adding body and also providing therapeutic astringent properties. Such starch may be of any suitable origin, for example, the starch may be maize starch, rice starch, potato starch, wheat starch, and may be incorporated in the preparation in the form of a gel. Such gel may be formed in any suitable manner, for example, the gel may be formed by steam heating an agitated mixture of starch and water.

One embodiment of the invention will now be described by way of example only.

Example:

A cream preparation is prepared by mixing the following constituents:—

	by weight
White Soft Paraffin Wax	9.5%
Emulsifying Wax (e.g. Lanbritol Wax N21)	7%
Chelating Agent (EDTA)	0.09%
Sodium Acid Phosphate	0.5%
Lactic Acid	0.5%
100% Hydrogen Peroxide	1.5%
Potassium 8-Hydroxyquinoline Sulphate	0.5%
Maize Starch	5.25%
Water	to 100%

The resulting preparation is a smooth oil-

in-water 'vanishing' cream having pH 2.6. The cream can be stored in tubes or other containers which should be opaque or of limited transparency to avoid decomposition in sunlight. The cream can be applied easily and smoothly to the skin and has good dermatological activity for example in the treatment of acne whilst being cosmetically acceptable. The cream does not tend to cause damage to skin tissue or undue irritation and is stable and retains its activity even after long storage. Any decomposition of the hydrogen peroxide merely produces water and does not give rise to the formation of any possibly harmful decomposition products.

In order to demonstrate that the preparation has anti-bacterial activity subsequent to manufacture thereof and subsequent to storage of the preparation, the following tests were performed on a four-month old sample of the preparation.

The cream was placed in wells on plates sown with different strains of different bacterial species. After incubation for 24—72 hours presence and sizes of inhibition zones were noted. The tests were performed on nutrient agar or brain heart infusion agar and also on blood agar which breaks down hydrogen peroxide and rapidly eliminates its anti-bacterial activity.

The results were as follows:—

Species	Proportion of Strains Inhibited: Nutrient Agar or Brain Heart Infusion Agar	Blood Agar
Staph. aureus	16/16	16/16
Str. pyogenes	6/6	6/6
Ps. aeruginosa	6/6	0/8
Coliform species	10/10	2/16
Diphtheroid species	8/8	8/8
Propionobacterium acnei	2/2	2/2
Clostridium welchi	2/2	2/2

The preparation gave wide zones of inhibition for all strains of all species tested using nutrient agar or brain heart infusion agar. Removal of hydrogen peroxide by the blood agar gave rise to elimination of anti-bacterial activity in respect of all *Psuedomonas aeruginosa* strains and most of the Coliform species strains. In the case of the other species anti-bacterial activity was retained, probably due to the presence of quinoline derivative, but the inhibition zones were reduced in size by about one half to two-thirds.

It can be seen therefore that the preparation contains hydrogen peroxide having utilisable antibacterial activity despite the incorporation of the hydrogen peroxide into the cream preparation and despite the storage of the preparation.

In the Example given above, the proportion of white soft Paraffin Wax may be varied between 1% and 38%, a corresponding change being made in the proportion of water.

Additionally or alternatively, it is possible to vary the proportion of hydrogen peroxide within a range having a preferred upper limit of 3.75%. A preferred range, however, is 0.75 to 2%. The proportion of water is correspondingly changed to allow for any variation.

Additionally or alternatively, it is possible to replace the quinoline derivative with 100% Chlorhexidine Gluconate, a range having an upper limit of 2% being preferred for this constituent and 0.5% being a particularly preferred proportion. The proportion of water is correspondingly changed to allow for any variation in this respect.

Additionally or alternatively, urea can be incorporated in the composition in any desired suitable proportion, provided that the proportion of white soft Paraffin Wax and emulsifying wax is less than the proportion of water in the formulation.

It will be noted that with the embodiment described above the hydrogen peroxide can be intimately incorporated in an emulsion in the cold. Incorporation in a warm mix presents problems due to the thermal instability of hydrogen peroxide. The incorporation into an emulsion of course facilitates spreading on the skin.

It is of course to be understood that the invention is not intended to be restricted to the details of this example composition. Thus, for example, a composition according to the invention need not be used for the treatment of acne, it may be used for the treatment of burns or for the treatment of any other suitable human or animal skin condition or for any other suitable dermatological purpose. Further, the composition need not incorporate auxiliary therapeutic agents (such as the quinoline derivative) but may comprise essentially only the hydrogen peroxide, oil medium, water and buffer.

Still further, the composition of the invention need not be a cream preparation but may be in the form of a gel or lotion.

WHAT WE CLAIM IS:—

1. A dermatological composition in the form of a cream, lotion or gel comprising an oil medium dispersed in an aqueous medium, said aqueous medium containing hydrogen peroxide and a buffer to maintain the pH of the composition at less that 7.

2. A composition according to claim 1 comprising up to 3.75% by weight hydrogen peroxide.

3. A composition according to claim 2 comprising 0.75% to 2% by weight hydrogen peroxide.

4. A composition according to any one of claims 1 to 3 having a pH of 2.5 to 6.5.

5. A composition according to any one of claims 1 to 4 wherein the oil medium comprises a saturated hydrocarbon wax and an emulsifying wax.

6. A composition according to any one of claims 1 to 5, wherein the buffer comprises any of lactic acid, citric acid, tartaric acid, maleic acid, hydroxysuccinic acid with an acid salt.

7. A composition according to claim 6, wherein the acid salt is any of sodium and potassium acid phosphate, sodium and potassium acid citrate, sodium and potassium acid tartrate.

8. A composition according to any one of claims 1 to 7. incorporating one or more of a chelating agent, starch, a pharmaceutically active quinoline derivative, chlorhexidine gluconate, urea, hydrocortisone, a corticosteroid.

9. A composition according to claim 8, incorporating said quinoline derivative which is any of potassium 8-hydroxyquinoline sulphate, 8-hydroxyquinoline sulphate, iodochlorhydroxyquinoline, diiodohydroxyquinoline, and di(8-hydroxy-7-iodoquinoline-5-sulphonate).

10. A composition according to claim 8 or 9, incorporating said chelating agent which is any of ethylenediamine tetraacetic acid and the disodium, trisodium, dipotassium and tripotassium salts of this acid.

11. A composition according to any one of claims 8 to 10, incorporating starch in the form of a gel.

12. A composition according to claim 1 substantially as hereinbefore described in the Example.

Agents for the Applicants,
SYDNEY E. M'CAW & CO.,
Chartered Patent Agents,
Saxone House,
52—56 Market Street,
Manchester M1 1PP.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.